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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,213	02/14/2002	Chung-Hsiun Wu	13062-002001	3100

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,213	WU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) *7 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-12,17-20,22-29,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 4/28/05 has been entered. Claims 21 and 30 have been canceled. Claims 1-20, 22-29, and 31-32 are pending in the instant application. Of these, claims 7 and 13-16 have been withdrawn as being drawn to subject matter non-elected without traverse. Claims 1-6, 8-12, 17-20, 22-29, and 31-32 are currently under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3-6, 8, 17, 19-20, 23-26, 29, and 32 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,462,254 (10/8/02), hereafter referred to as Vernachio et al., is withdrawn in view of applicant's amendments to the claims. However, please note that applicant's amendment have resulted in new grounds of rejection of these claims under 35 U.S.C. 103 below.

Claim Rejections - 35 USC § 103

The rejection of claims 2, 10-11, 18, 21-22, 27-28, and 30-31 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,462,254 (10/8/02), hereafter referred to as Vernachio et al., in view of U.S. Patent No. 5,726,044 (3/10/98), hereafter referred to as Lo et al., is withdrawn over claims 2, 10-11, 18, 21, and 30 in view of applicant's cancellation or amendment of the claims, and **maintained or newly applied to amended claims 20, 22-29, and 31-32**. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the grounds of rejection for reasons of record as discussed in detail below.

The rejection of record is reiterated for clarity. Vernachio et al. teaches methods of isolating and concentrating a fusion protein which comprises a capture tag, a polypeptide sequence of interest, and a detection tag comprising administering to a mammal a nucleic acid encoding a fusion protein comprising a capture tag sequence, a polypeptide sequence of interest, and a detection tag sequence and capturing the fusion protein from a sample from the mammal with an antibody that specifically binds to the capture tag sequence (Vernachio et al., columns 4, 7, and 13-14, see claims 1-15). The capture tag sequence is the "second amino acid sequence" of the fusion protein and the "first member of a specific binding pair", while the antibody which recognizes the capture tag is the "second member of the specific binding pair". Vernachio et al. further teaches that the capture tag can be a peptide more than 5 amino acids long, see column 14, claim 3; and that the antibody can be a monoclonal antibody, see column 5, lines 51-56). Vernachio et al. also teaches the immobilization of the fusion protein to a solid surface such as a membrane, microtiter dish, or magnetic bead (Vernachio et al., column 6, lines 57-67). In addition, Vernachio et al. teaches that the sample from the mammal containing the fusion protein

can be serum or a tissue lysate (Vernachio et al., column 11, lines 28-37, and column 12, lines 25-67).

Vernachio et al. differs from the instant invention by not teaching that the capture tag sequence is an Fc domain of an immunoglobulin. Vernachio et al. however teaches that the capture tag sequence is a sequence of amino acids that specifically binds to a ligand such as an antibody (Vernachio et al., column 2, lines 20-21, and column 2). Vernachio et al. further teaches that the particular capture tag sequence is not critical to the invention, and that the capture tag is chosen for its ability to concentrate the fusion protein (Vernachio et al., column 5, lines 11-16). Lo et al. provides motivation for using an Fc region of an immunoglobulin as a "capture tag sequence" in the fusion protein provided by Vernachio. Lo et al. teaches nucleic acid vectors for expressing a fusion protein in mammalian cells wherein the fusion protein comprises an Fc region of an immunoglobulin linked by a protease cleavage site to a selected target polypeptide (Lo et al., columns 3-4). Lo et al. further teaches that the presence of the Fc region of an immunoglobulin in the fusion protein allows for increased production of the target protein and ease of collection because the secreted fusion protein can be collected without the need for cell lysis and can be purified using common reagents including antibodies and protein A (Lo et al., column 2, especially lines 29-35, and column 3, lines 9-23). Lo et al. further teaches the advantages of including the protease cleavage site in the fusion protein because the polypeptide of interest can be easily separated from the Fc region used to purify the fusion protein (Lo et al., columns 3 and 9). Note as well that Lo et al. teaches that protease inhibitors can also be administered to prevent cleavage of the fusion protein by proteases (Lo et al., column 16). Thus, based on the motivation to include the Fc region of an immunoglobulin and a protease cleavage

site in a fusion protein in order to facilitate and improve the purification of the fusion protein as taught by Lo, and based on the teaching of Vernachio et al. that the "capture tag sequence" should be selected based on its ability to concentrate the protein, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the Fc region linked to a protease cleavage site as taught by Lo et al. as the "capture tag sequence" in the fusion proteins taught by Vernachio et al. Furthermore, in view of the successful use of the Fc region to purify fusion proteins as taught by Lo et al., and the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in modifying the vectors encoding a fusion protein taught by Vernachio et al. to include the nucleic acid sequence encoding the Fc region and the protease cleavage site as taught by Lo et al.

The applicant argues that there is no motivation to combine the teachings of Lo et al. with those of Vernachio et al. since the operability of the Vernachio method requires the presence of an intact fusion protein to identify the fusion protein after it has been captured using the detection tag sequence. In response, there is no requirement in Vernachio that the capture tag remain on the fusion protein for protein detection. Vernachio teaches that the capture tag is used to purify the fusion protein from tissue culture or from tissue or organs removed from a genetically engineered mammal (see columns 3-6). Once the fusion protein has been purified, Vernachio teaches that it can be used for a variety of purposes, including the use of the fusion protein in detection assays, or the use of the protein for therapy (see columns 8-9). In regards to detection methods, Vernachio teaches many methods that do not require the presence of the capture tag, including agglutination assays and western blots (see column 8). Thus, Vernachio does not teach that the capture tag must be retained in order for the protein to be detected.

Regarding Lo et al., Lo teaches using an Fc region as the "capture tag" in a fusion protein and further provides motivation for removing the capture tag by protease cleavage. Specifically, Lo teaches that the Fc region has certain effector functions which it might be advantageous to remove before using the polypeptide of interest contained in the fusion protein as a therapeutic molecule. As Vernachio teaches that the polypeptide of interest in the fusion protein is useful for therapeutic purposes, the skilled artisan would have been motivated to follow the teachings of Lo to include a protease cleavage site between the polypeptide of interest and the "capture tag" used to purify the fusion protein. Therefore, the rejection of record stands.

The rejection of claims 9 and 12 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,462,254 (10/8/02), hereafter referred to as Vernachio et al., in view of U.S. Patent No. 5,726,044 (3/10/98), hereafter referred to as Lo et al. , as applied to previously pending claims 2, 10-11, 18, 21-22, 27-28, and 30-31, and further in view of US Patent No. 5,703,055 (12/30/97), hereafter referred to as Felgner et al., is withdrawn in view of applicant's amendments to the claims.

Claims 1-6, 8, 10-11, and 17-19 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,462,254 (10/8/02), hereafter referred to as Vernachio et al., in view of U.S. Patent No. 5,726,044 (3/10/98), hereafter referred to as Lo et al. , as applied to claims 20, 22-29, and 31-32 above, and further in view of Brown et al. (1998) Prot. Express. & Purif., Vol. 14, 120-124.

The claims as amended recite methods of screening to identify target binding molecules comprising administering to a mammal a nucleic acid encoding a fusion protein which contains a first amino acid sequence and a second amino acid sequence, wherein the second amino acid sequence contains a first member of a specific binding pair, removing a biological sample from the mammal that contains the fusion protein, isolating the fusion protein by binding second member of the specific binding pair to the fusion protein, further contacting the fusion protein with a collection of target binding molecules and identifying one or more target binding molecules form the collection that binds to the first amino acid sequence of the fusion protein.

As discussed in detail above, the combined teachings of Vernachio et al. in view of Lo et al. provide motivation and a reasonable expectation of success for methods of purifying a fusion protein comprising a polypeptide of interest and a "capture tag" such as the Fc region of an immunoglobulin by administering to a mammal a nucleic acid encoding a fusion protein comprising a capture tag sequence, such as the Fc region of an immunoglobulin, and a polypeptide sequence of interest, and capturing the fusion protein from a sample from the mammal with an antibody that specifically binds to the capture tag sequence (Vernachio et al., columns 4, 7, and 13-14, see claims 1-15).

However, while Vernachio et al. and Lo et al. both teach the polypeptide of interest can be used in detection assays or as therapeutic molecules, neither reference teaches using the fusion protein comprising the polypeptide of interest and the Fc region of an immunoglobulin to identify a molecule which binds to the polypeptide of interest from a collection of target binding molecules. Brown et al. supplements Vernachio et al. and Lo et al. by teaching that purified fusion proteins comprising a polypeptide of interest and the Fc region of an immunoglobulin can

be used to screen for phage-displayed peptides or ligand specific drugs (Brown et al., pages 123-124, particularly, the bridging paragraph). Based on the motivation provided by Brown et al. that fusion proteins comprising a polypeptide of interest and the Fc region of an immunoglobulin can be used to screen for binding molecules specific for the polypeptide of interest in a collection of binding molecules, i.e. through phage display, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the fusion protein produced by the methods of Vernachio et al. and Lo et al. to screen for binding molecules specific for the polypeptide of interest. Further, based on the statements in Brown et al. that such fusion proteins were in fact successfully used to screen a phage display peptide library, the skilled artisan would have had a reasonable expectation of success in using fusion proteins comprising the Fc region of immunoglobulin to identify target binding molecules.

Claim Rejections - 35 USC § 112

The rejection of claims 17-18 and 29-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of the cancellation of claim 30 and the amendments to claims 17-18, 29, and 31.

Claims 8-9 and 11-12 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 8-9 and 11-12 lack antecedent basis for "the target binding molecule". Claims 8-9 and 11-12 depend on claims 1 and 2. Claims 1 and 2 have been

amended to recite "target binding molecules". While there exists antecedent basis for the plural, "target binding molecules", there is no antecedent basis for the singular, "target binding molecule".

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official

communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER